





NCI Division of Cancer Biology Strategic Workshop

Prospective Outlook of Mechanics in Oncology

Executive Summary, Agenda, and Participants List

September 11-12, 2014

NCI Shady Grove, Terrace Room TE406 9609 Medical Center Drive, Rockville, MD 20850

Division of Cancer Biology
National Cancer Institute
National Institutes of Health
U.S. Department of Health and Human Services

EXECUTIVE SUMMARY

The National Cancer Institute (NCI) Physical Sciences in Oncology Initiative within the Division of Cancer Biology (DCB) aims to enrich our current understanding of cancer by facilitating the formation of teams of physical scientists and cancer researchers who work together to bring a novel "physical sciences perspective" to cancer biology. On September 11-12, 2014, DCB convened a Strategic Workshop: **Prospective Outlook of Mechanics in Oncology** to provide a status update of the field of cell and tissue mechanics in cancer biology and to address the prospect of using mechanical measurements as physical biomarkers for disease progression or treatment response.

The response of cancer cells and tissues to physical forces, pressures, or molecular tensions in the stromal microenvironment is a function of their inherent architectural and structural properties. Cell and tissue mechanics is defined as the physical properties, the strength of mechanical forces, and the resultant cell and tissue functional response. Mounting evidence suggests cell and tissue mechanics are significant contributors to the initiation and progression of cancer. The propagation of mechanical forces at cellular and tissue scales has been associated with numerous cell processes, including differentiation, migration, and proliferation. Changes to the physical properties of cells, extracellular matrix, or tissue during cancer progression perturb these mechanical forces and subsequently affect downstream cellular processes. Therefore, knowledge of the mechanisms involved in mechanical feedback loops and application of appropriate mechanical measurement tools may lead to new potential drug targets, diagnostic tools, and risk indicators in oncology. This workshop was designed to explore the latest research in the field of cell and tissue mechanics in cancer biology and identify opportunities as next steps for the field.

Workshop discussions centered around findings pertaining to the mechanical measurements of single cells, mechanical forces between neighboring cells, as well as between cells and their surrounding matrix. Presentations highlighted the effects of mechanical forces on cancer progression, correlations between cell mechanical properties and molecular expression pathways, and assessments of how changes in the extracellular matrix structure and physical properties and may correlate with tumor progression. Two broad topics were identified as emerging areas for more development. These included (1) the interplay between mechanical forces and cancer pathways, and (2) the development of physical biomarkers for defining "signatures" of cancer progression. Below is a summary of the research results presented in the two highlighted topic areas and potential opportunities for moving the field forward.

Interplay between mechanical forces and biological pathways

- Induction of mechanical pressure in vivo activates oncogenic signaling pathways in mouse models of cancer
- Mechanical stress in fibronectin induces expression of soluble factors that promote angiogenesis and tumor formation
- Pro-inflammatory pathways modulate matrix stiffness and drive tumor progression
- Dynamic shear forces and cellular crowding influence adhesion molecule-mediated migration of metastatic tumor cells in a 3D context
- Matrix stiffness affects the viscosity and elasticity of the cell nucleus, which leads to susceptibility of cells to DNA damage and activation of oncogenic signaling pathways

Biophysical markers for tumor progression signatures and diagnostics

- Mechanophenotyping of circulating tumor cells (i.e., cell size, contractility, deformability, morphology, adhesiveness) enables more sensitive, objective, and efficient diagnosis of tumor cell malignancy
- Mechanical waves in magnetic resonance elastography image tissue stiffness *in vivo* (human and mouse) and determine distinct tumor types based on tissue stiffness signatures

- Biomechanical measurements distinguish between cancerous and normal tissue by quantifying cell-cell adhesion/surface tension and cell stiffness from the single-cell scale to tissue scale
- Cell-matrix traction forces and adhesion strength measurements define adhesive force signatures that are unique to distinct cancer cell types (e.g., tumor-initiating cells, cancer stem cells, cell subpopulations within a heterogeneous tumor)
- Collagen remodeling signatures defined by structural properties are potential prognostic indicators in cancer (*i.e.*, higher degree of collagen fiber alignment perpendicular to the tumor boundary is indicative of tumor progression)

Next steps to advance the field of cell and tissue mechanics

- Increased collaboration between the mechanics/mechanobiology and oncology communities in order to better identify immediate clinical needs as well as developing better methods for incorporating cell and tissue mechanical measurements into clinical practice
- Development of standardized cell lines and standardized synthetic matrix analogs with precise control over biophysical and biochemical properties to improve studies of cell-cell and cell-matrix mechanics in 3D cultures
- Development of more robust technologies to better understand the connection between mechanical forces and cellular processes such as molecular pathways and regulation, transcription, translation, genome editing, and phenotype
- Integration of measurements taken at different time- and length-scales into more comprehensive datasets and incorporating them with mathematical approaches; and the use of mathematical modeling to better understand the feedback loop of mechanical and biological information
- Better understanding of the effect of anti-cancer drugs, chemotherapy and radiation on the physical properties of the stroma
- Identification of new biomechanical markers that have prognostic value
- Addressing the dynamic complexity of cancer (e.g., tumor heterogeneity, etc.) when developing new cell
 and tissue mechanics models
- Development of clinically relevant animal models for studying cell and tissue mechanics in vivo
- Incorporating physical factors in addition to stiffness, such as topology and spatial features within tumor tissues, to better understand the specific physical parameters and how they affect cancer biology.







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AGENDA

Meeting Objectives

Over the last decade, mounting evidence has identified cell and tissue mechanics as a contributor in the initiation and progression of cancer. Mechanical forces exchanged at a cellular and tissue level have been associated with numerous cell processes, including differentiation, migration, proliferation, and adhesion. Changes to the physical properties of cells, extracellular matrix, or tissue during disease progression perturb these mechanical forces and subsequently affect downstream cellular processes. Early knowledge of the mechanisms involved in mechanical feedback loops and application of appropriate mechanical measurement tools may lead to new potential drug targets, diagnostic tools, and risk indicators in oncology.

This workshop will serve to provide a status of the field of cell and tissue mechanics in understanding cancer biology and the prospect of using mechanical measurements as physical biomarkers for disease progression or treatment response. Discussions will revolve around the mechanisms of cancer cell response to mechanical forces, the types of mechanical measurements that are appropriate for monitoring mechanical forces, and the potential translation of mechanical biomarkers.

Day 1: Thursday, September 11

3:00 p.m. - 3:30 p.m. Security and Registration

3:30 p.m. - 3:35 p.m. Welcome and Introductions

Larry A. Nagahara, Ph.D.

Associate Director, Division of Cancer Biology

National Cancer Institute

3:35 p.m. - 3:45 p.m. Workshop Goals

Nicole M. Moore, D.Sc.

Program Director, Division of Cancer Biology

National Cancer Institute

3:45 p.m. - 6:30 p.m. Session I: Quantifying Mechanical Forces

Moderator: Jennifer Couch, Ph.D.

Chief, Structural Biology and Molecular Applications Branch

Division of Cancer Biology National Cancer Institute 3:45 p.m. - 4:10 p.m. Cell and Tissue Mechanics

Josef Käs, Ph.D.

Principal Investigator and Head, Soft Matter Physics Division, Institute of Experimental

Physics 1

University of Leipzig

4:10 p.m. - 4:35 p.m. Fluid Stresses Govern 3D Cell Migration

Roger D. Kamm, Ph.D.

Cecil and Ida Green Distinguished Professor of Biological and Mechanical Engineering

Massachusetts Institute of Technology

4:35 p.m. -5:00 p.m. **ECM Tension and Topology**

Delphine Gourdon, Ph.D.

Assistant Professor, Department of Materials Science and Engineering

Cornell University

5:00 p.m. – 5:25 p.m. Integrin Tension and Cell Adhesion

Andrés Garcia, Ph.D.

Rae S. and Frank H. Neely Chair and Regents' Professor, George W. Woodruff School

of Mechanical Engineering Georgia Institute of Technology

5:25 p.m. - 6:30 p.m. **Group Discussion**

6:30 pm - 7:00 p.m. Shuttle return for travelers to Gaithersburg Marriott Washingtonian

Dinner (on own)

Day 2: Friday, September 12

7:30 a.m. Shuttle pickup for travelers at Gaithersburg Marriott Washingtonian

8:15 a.m. - 8:20 a.m. **Welcome Day 2**

Nastaran Z. Kuhn, Ph.D.

Program Director, Division of Cancer Biology

National Cancer Institute

8:20 a.m. - 9:15 a.m. Session II: Standardizing Mechanics Measurements

Moderator: Nicole M. Moore, D.Sc.

Program Director, Division of Cancer Biology

National Cancer Institute

8:20 a.m. - 8:45 a.m. Summary of the UN of Cell Modulus Project

Denis Wirtz, Ph.D.

Theophilus Halley Smoot Professor of Chemical and Biomolecular Engineering

Johns Hopkins University

8:45 a.m. - 9:15 a.m. **Group Discussion**

9:15 a.m. - 11:40 a.m. Session III: Biological Responses to Mechanical Forces

Moderator: Suresh Mohla, Ph.D.

Associate Director, Division of Cancer Biology Chief, Tumor Biology and Metastasis Branch

National Cancer Institute

9:15 a.m. - 9:40 a.m. Force Driven Tumorigenesis

Emmanuel Farge, Ph.D.
Research Director INSERM

Institute Curie

9:40 a.m. - 10:05 a.m. Biological Response to ECM Stiffness

Patricia Keely, Ph.D.

Professor and Chair, Cell and Regenerative Biology

University of Wisconsin – Madison

10:05 a.m. – 10:20 a.m. **Break**

10:20 a.m. -10:45 a.m. Mechanically Coupled Systems of Mammary Acini

Jan Liphardt, Ph.D.

Associate Professor of Bioengineering

Stanford University

10:45 a.m. -11:10 a.m. Nuclear Mechanics and DNA Stability

Dennis Discher, Ph.D.

Robert D. Bent Chaired Professor, School of Engineering and Applied Science

University of Pennsylvania

11:10 a.m. - 11:40 a.m. **Group Discussion**

11:40 a.m. - 1:00 p.m. **Lunch** (on own)

12:15 p.m. - 1:00 p.m. Poster Viewing in Terrace Room TE406

1. Dexamethasone Increases Tissue Surface Tension and Reduces Dispersal of Primary Glioblastoma Cells

Ramsey Foty, Ph.D., Associate Professor, Biomedical Engineering, Rutgers University-Robert Wood Johnson Medical School, Department of Surgery

2. Mechanobiology of the Cellular Glycocalyx

Matthew Paszek, Ph.D. Assistant Professor, Chemical and Biomolecular Engineering, Cornell University

3. Screening Cancer Cell Mechanotype by Parallel Microfiltration

Amy Rowat, Ph.D., Principal Investigator, Integrative Biology and Physiology, University of California, Los Angeles

4. Biomaterials Based Adaptive Tumor microenvironments for Lymphoma

Ankur Singh, Ph.D. Assistant Professor, Mechanical and Aerospace Engineering, Cornell University

5. Extracting Quantitative Data from AFM Indentations on Soft, Heterogeneous Biomaterials

J. Rory Staunton, Research Assistant, Center for Biological Physics, Arizona State University

6. MDA-MB-231 Cells Stiffen During Invasion into 3D Collagen I Matrices

J. Rory Staunton, Research Assistant, Center for Biological Physics, Arizona State University

1:00 p.m. - 2:45 p.m. Session IV: Translational Potential of Mechanics in Oncology

Moderator: Jerry S.H. Lee, Ph.D.

Deputy Director, Center for Strategic Scientific Initiatives

National Cancer Institute

1:00 p.m. - 1:25 p.m. **Mechanical Drug Targets and Prognostic Indicators**

Valerie Weaver, Ph.D.

Professor of Surgery, Anatomy, Bioengineering & Tissue Regeneration and

Therapeutic Sciences

Director, Center for Bioengineering and Tissue Regeneration

University of California, San Francisco

1:25 p.m. - 1:50 p.m. Diagnosis of Malignant Pleural Effusions by Single-Cell Mechanophenotyping

Dino DiCarlo, Ph.D.

Associate Professor, Department of Bioengineering

University of California, Los Angeles

1:50 p.m. - 2:15 p.m. Magnetic Resonance Elastography

Richard Ehman, M.D. Professor of Radiology

Mayo Clinic

2:15 p.m. - 2:45 p.m. **Group Discussion**

2:45 p.m. – 2:55 p.m. **Break**

2:55 p.m. - 3:30 p.m. Session V: Overview and Future Directions

Moderators: Nicole M. Moore, D.Sc.

Program Director, Division of Cancer Biology

National Cancer Institute

Nastaran Z. Kuhn, Ph.D.

Program Director, Division of Cancer Biology

National Cancer Institute

3:30 p.m. Adjourn

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